Patent Application
Attorney Docket No. PC10408A

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By _____
(Signature of person mailing)
Jason G. Tebbutt
(Typed or printed name of person)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Susan B. Sobolov-Jaynes :
Examiner: Jarvis, W.

APPLICATION NO.: 09/707,320 :
Group Art Unit: 1614

FILING DATE: November 7, 2000 :

TITLE: COMBINATION TREATMENT FOR DEPRESSION AND ANXIETY :

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RULE 132 DECLARATION

Stafford McLean hereby, declares, states and says that:

1) He received a Ph.D. from Princeton University

2) He is currently employed by Pfizer Inc in Pfizer's Research and Development Division as a Research Fellow in the Department of Neuroscience in Bldg 220 Rm 4471 and he has worked as a research scientist at Pfizer for 19 years

3) He is familiar with the subject matter of the above identified application and the references cites therein and was a principal investigator directing both *in vitro* and *in vivo* research involving NK_1 receptors. An in vivo model relevant to anxiety and obsessive compulsive disorder was established to assess the effects of antagonists of the NK_1 receptor, Serotonin Reuptake Inhibitors and their combination, therein. Rodents, using the bedding material in their cages, will bury noxious materials and this burying behavior is inhibited by agents with anxiolytic activity. This burying behavior extends to "harmless" object and is blocked by anxiolytic agents, as well. The SRI, sertraline, is active in this model producing a maximal effect at 32 mg/kg, s.c. Similarly, an NK_1 receptor antagonist is active in the model with a maximal effect at 32 mg/kg, s.c.

Combination of said agents at lower doses that are modestly active results in a maximal blockade of the burying behavior. This suggests the opportunity to combine agents with NK_1 activity and agents with serotonin reuptake activity either as separate drugs or combined into a single molecule to produce robust anxiolytic activity. Furthermore, reduction in dose/activity of each agent may reduce the likelihood of unwanted side effects.

4) Further declarant sayeth not.

He further declares that all statements made herein of his own knowledge are true and all statements made on information and belief to be true. All statements made herein are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code, and that willful false statements may jeopardize the validity of the above application or any patent that may issue from it.

Date: 9-15-05

Stafford McLean

Date: June 15, 2005

Male ICR mice (17-19 g) upon arrival were grouped housed (10/box) and allowed to habituate to the vivarium for approximately 1 week. On the day of the study, mice were numbered (tail), weighed and injected with drug of interest. Thirty minutes later, mice were placed in a small mouse box (11.5 x 7.25 x 4.75") which had 25 marbles that were equally spaced on top of ~5 cm of sawdust bedding. Mice were allowed to explore/bury for 30 minutes. At the end of time, mice were removed from the box and the number of marbles that were at least 1/3 way visible were counted and recorded. Data is expressed as the number of marbles buried (not visible). Immediately after removing mice from the box, they were placed 5 at a time on a wire grid to measure the degree to which they might be behaviorally impaired. The grid was then inverted for 45 seconds. The mice were rated as either falling off (0), hanging on (1) or climbed on top (2). This measure was done as an indicator of impairment/sedation. Experimenter was blind to drug conditions until end of study and groups were distributed evenly throughout the rack.

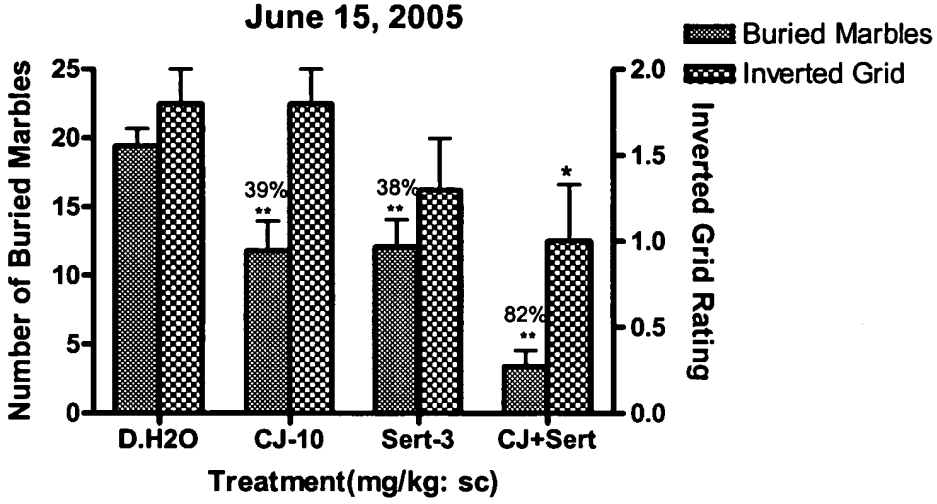
Drugs/doses: **CJ-011974-01 (10 mg/kg;sc) and/or Sertraline (3 mg/kg;sc)**
Route of Admin: **SC**
Vehicle: D. H2O
Pre-treat: **30 minutes for MB & 60 min for IG**
Comments:

Mouse #	**Vehicle**		**CJ-11974**		**Sertraline**		**CJ+Sert**	
	marble	grid	marble	grid	marble	grid	marble	grid
1	21	2	18	2	17	2	11	2
2	19	2	9	2	7	2	8	2
3	23	2	21	2	12	0	0	0
4	21	2	2	0	16	1	4	2
5	17	0	9	2	6	0	4	0
6	17	2	21	2	12	2	3	0
7	20	2	16	2	0	2	0	0
8	10	2	7	2	14	0	1	2
9	23	2	4	2	22	2	3	2
10	23	2	11	2	15	2	0	0
Mean	19.4	1.8	11.8	1.8	12.1	1.3	3.4	1.0
SEM	1.3	0.2	2.2	0.2	2.0	0.3	1.2	0.3
Sig from Veh			$		$		$	$
% inhibition			39%		38%		82%	

Conclusion: Previous work has shown a dose-dependent decrease in marble burying by sertraline and CJ-11974, an NK_1 receptor antagonist. Such decrease is consistent with the activity exhibited by other anxiolytics in this assay and is consistent with the anxiolysis observed with these two agents in the clinic. Combined dosing of sertraline and CJ-11974, at doses that when given alone produce only a modest effect, provides a near maximal response. This is consistent with an additive response. As seen in the graphical representation of the data (below) the combined doses also produce a

significant effect on the inverted grid suggesting some impairment of sensorimotor function. The contribution of this to the reduction in marble burying will be further explored.

Effects of CJ-11974 and/or Sertraline on Marble Burying Behavior & the Inverted Grid in Male ICR Mice
June 15, 2005



* p< 0.05; **p<0.01 vs. appropriate vehicle control
n=10